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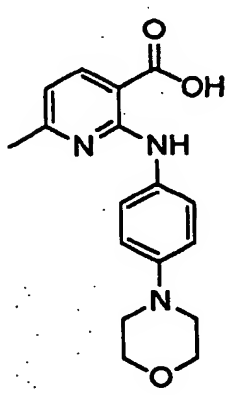
(54) Title: 6-METHYLPYRIDINE DERIVATIVES, METHOD FOR PREPARING THEREOF AND ANTIVIRAL PHARMACEUTICAL COMPOSITION COMPRISING THE SAME



(I)

(57) Abstract: The present invention relates to 6-methylpyridine derivatives useful as an antiviral agent. More particularly, the present invention relates to novel 6-methylpyridine derivatives having an excellent inhibitory effect on replication of Hepatitis C virus (HCV), or pharmaceutically acceptable salts thereof, to a method for preparing thereof, and to an antiviral pharmaceutical composition comprising the compound as an active ingredient. The 6-methylpyridine derivatives of the present invention have an excellent inhibitory effect on replication of hepatitis C virus and thus can be advantageously used as a therapeutic or prophylactic agent of hepatitis C.

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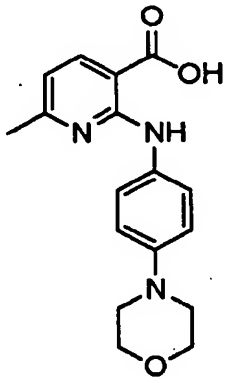
6-METHYLPYRIDINE DERIVATIVE, METHOD FOR PREPARING THEREOF AND ANTIVIRAL PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

Field of the Invention

The present invention relates to 6-methylpyridine derivatives useful as an antiviral agent. More particularly, the present invention relates to novel 6-methylpyridine derivatives having an excellent inhibitory effect on replication of Hepatitis C virus (HCV), represented by the following formula I:



or pharmaceutically acceptable salts thereof, to a method for preparing thereof, and to an antiviral pharmaceutical composition comprising the compound as an active ingredient.

Description of the Related Art

Hepatitis C virus (HCV) is the major etiological agent of non-A and non-B viral hepatitis, mainly being post-transfusion and community-acquired. Once infected with HCV, approximately 80% of infected people, given its symptom is manifested, progress to chronic hepatitis, and the rest 20% of infected people progress to acute hepatitis causing hepatic cirrhosis, which is eventually transferred to liver cancer. According to a recently published report, more than 2

hundred million worldwide are infected with HCV. For instance, more than 4.5 million Americans are infected with the same virus (The number is likely to be 15 million in maximum.) and more than 5 million Europeans are HCV patients.

HCV is a member of the *Flaviviridae* family. More specifically, HCV has about 9.5kb sized (+)- RNA (single stranded positive-sense RNA) genome inside its membrane. RNA genome consists of an untranslational region at 5'and 3' ends (UTR) and a long open reading frame (ORF). This ORF is expressed as a polyprotein including 3,100 to 3,040 amino acids by host cell enzymes and divided into 3 structural proteins and 6 nonstructural proteins by the host cell enzymes and its own protease. Also, there is a uniformly conserved region in the 5' end and the 3' end of the genome, respectively. This region is believed to play an important role for protein formation of the virus and RNA replication.

The long strand ORF is expressed as a polyprotein, and through co-translational or post-translational processing, it is processed structural proteins, i.e. core antigen protein (core) and surface antigen protein (E1, E2), and nonstructural proteins, i.e. NS2 (protease), NS3 (serine protease, helicase), NS4A (serine protease cofactor), NS4B (protease cofactor, involved in resistance), NS5A, and NS5B (RNA dependent RNA polymerase, RdRp), each contributing to proliferation of virus. The structural proteins are divided into core, E1, and E2 by signal peptidase of the host cell. Meanwhile, the nonstructural proteins are processed by serine protease (NS3) of the virus and cofactor (NS2, NS4A, and NS4B). The core antigen protein together with surface antigen protein of the structural protein compose a capsid of the virus, and the nonstructural proteins like NS3 and NS5B play an important part of the RNA replication of the virus (Referencc: Bartenschager, R., 1997, Molecular targets in inhibition of hepatitis C virus replication, *Antivir. Chem. Chemother.* 8: 281-301).

Similar to other flaviviruses, the 5' and 3' ends of the virus RNA has a

uniformly conserved untranslational region (UTR). Generally, this region is known to play a very important role in replication of the virus. The 5′ end has 5′-UTR composed of 341 nucleotides, and this part has the structure of 4 stem and loop (I, II, III, and IV). Actually, this functions as an internal ribosome entry site (IRES) necessary for translation processing to express protein. Particularly, the stem III, which has the biggest and most stable structure with conserved sequence, has been reported to play the most essential part for ribosome binding. In addition, a recent study tells that the virus proteins are expressed by disclosing translation processing from AUG that exists in the single RNA of the stem IV (Reference: Stanley, M. Lemon and Masao Honda, 1997, Internal ribosome entry sites within the RNA genomes of hepatitis C virus and other Flaviviruses, seminars in *Virology* 8:274-288).

Moreover, the 3′ end has 3′-UTR composed of 318 nucleotides. This part is known to play a very important role in the initiation step of binding of NS5B, an essential enzyme of RNA replication. 3′-UTR, according to the sequence and tertiary structure, is composed of three different parts: -X-tail-5′ starting from the 5′end to 98th nucleotide (98nt), -poly (U)- having UTP consecutively, and the rest of 3′-UTR-. More specifically, X-tail-5′ part consists of 98 nucleotides having a very conserved sequence, and has three stem and loop structures, thereby forming a very stable tertiary structure. Probably, this is why X-tail-5′ part is considered very essential of NS5B binding. Also, -poly (U)- part has a function of pyrimidine track, facilitating RNA polymerase effect. Lastly, the rest part of 3′-UTR part has the tertiary structure of loop and plays an important role in NS5B binding. However, its structure is known somewhat unstable. Overall, the 3′end region of HCV RNA is known to have an essential structure in NS5B binding (Reference: Yamada *et al.*, 1996, Genetic organization and diversity of the hepatitis C virus genome, *Virology* 223:255-281).

Among other enzymes of HCV, NS5B is the one that is directly involved in RNA replication and thus it is very important. NS5B consists of 591 amino acids having the molecular weight of about 68kDa. According to amino acid sequence, it is divided into 6 genotypes including 1a and 1b, and activated for RNA polymerization and terminal transferase. There are two RNA-binding domains, i.e. RBD1 and RBD2, in the NS5B enzyme. RBD1 exists between the amino acid numbers 83 and 194, and RBD2 exists between the amino acid numbers 196 and 298. Meanwhile, essential motif amino acids for RNA binding and activity are 'Asp' (amino acid number 220), 'Gly' (amino acid number 283), 'Gly' (amino acid number 317), 'Asp' (amino acid number 318), 'Asp' (amino acid number 319), and 'Lys' (amino acid number 346). Further, provided that there exists a RNA template of the virus itself, this enzyme can lead a polymerization reaction without another primer (Reference: Lohmann, V. *et al.*, 1997, Biochemical properties of hepatitis C virus NS5B RNA dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity, *J. viral.* 71:8416-8428).

RNA genome of HCV was isolated back in 1989 by molecular cloning (Reference: Choo, Q-L, *et al.*, 1989, Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 244:359-362). Although there have been a number of molecular biological researches on HCV from that point, there were always limitations due to lack of more effective cell culture systems and animal models. Fortunately, the above problem has been somewhat resolved by the introduction of a hepatoma cell line which made it possible to replicate HCV more stably (Reference: Lohmann, V., F. Korner, J-O Koch, U. Herian, L. Theilmann, R. Bartenschlarger, 1999, Replication of subgenomic hepatitis c virus RNAs in a hepatoma cell line. *Science* 285:110-113).

So far, no one has actually found vaccine or therapeutics that is very

effective for HCV. Hence, many pharmaceutical companies and institutes around the world are now trying to develop therapeutics and prevention of hepatitis C. HCV patients are prevalent in the world, and its frequency to be progressed to hepatic cirrhosis and/or liver cancer is much higher than HBV. Also, despite its high frequency to be progressed to chronic hepatitis, the research on infection mechanism of the virus is still under progress. People are infected with HCV through blood transfusion or medication via phleboclysis or tattooing, but most of cases HCV infection takes place through a direct blood contact. However, 40-50% of the HCV patients still do not exactly know how they became infected. Unfortunately, when people are infected with HCV through other channels besides the above, they are most likely progressed to chronic hepatitis and hepatic cirrhosis and eventually liver cancer. In view of this situation, it is a very urgent matter to develop a new vaccine and therapeutics to treat the diseases. In general, HCV is found because of diverse genotypes between strains and mutation. Once a person is progressed to chronic hepatitis from HCV, it is not hard to see reinfection or coinfection owing to genetic variants. Because of this, few succeeded to develop an effective vaccine for HCV. Another example of HCV treatments is using alpha interferon (α-interferon). However, this approach proved to be not that good because the effects of alpha interferon on different HCV genotypes were very diverse and when its administration was discontinued, patients relapsed into hepatitis C in most of cases. Hence it will be important to develop an inhibitor that binds only to a particular HCV protein in order to control HCV replication. The best targets of such research are HCV's NS3 protease/helicase and NS5B RNA polymerase of HCV. These enzymes are very useful for developing anti-HCV agent since these types of enzyme is not necessary for the host cell but essential for its own replication. In other words, NS5B of HCV (RNA dependent RNA polymerase (replicase) is an essential motif

for HCV, and this makes the enzyme a good target for suppressing the replication of HCV.

Now that HCV is not easily treated by vaccine, a new therapy using α-interferon and Ribavirin was introduced. But this, too, caused side effects and was not effective for treating hepatitis C. For example, about 25% of HCV patients showed no reaction to the interferon therapy, and about 25% reacted to it only for temporarily and relapsed into hepatitis C. The rest 50% of the patients maintained ALT at a normal level after the treatment was completed and their HCV RNA became negative. However, 50% of them relapsed into hepatitis C within 3-6 months. In short, only 25% of the HCV patients showed sustained response for more than 6 months. Meanwhile, the most HCV subtype found in patients' worldwide is 1 (1a, 1b) that is not easily treated by interferon, compared to 2 and 3 subtypes. In case of combination therapy with interferon and ribavirin, the treatment effect was doubled. What is known about ribavirin is that when it was used alone, it showed little effect on HCV and rather, caused side effects like erythroclastic anemia. Thus ribavirin was prescribed only when the interferon therapy was no good or HCV C relapsed again. So far, no one actually developed an antiviral agent for treating hepatitis C by suppressing the replication of HCV.

The present invention, therefore, is directed to develop a non-nucleoside compound having little toxicity and side effect but manifesting excellent anti-virus activity against HCV, by studying any possible compound that inhibits the activity of the recombinant HCV RNA polymerase (NS5B, RNA polymerase).

After making so much efforts for developing a compound with excellent anti-virus activity against HCV as an attempt to develop a new HCV therapeutics having little toxicity and side effect, the inventors finally succeeded to prepare a new 6-methylpyridine derivative represented by the above chemical formula 1 and

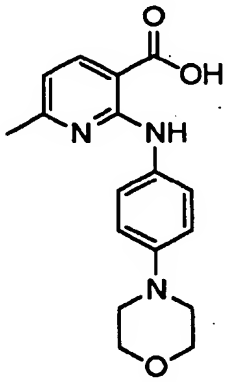
proved that these compounds are indeed very effective for inhibiting the replication of HCV.

Disclosure of Invention

It is, therefore, an object of the present invention to provide 6-methylpyridine derivatives, which are effective for inhibiting hepatitis C virus (HCV), and pharmaceutically acceptable salts and a method for preparing the compounds.

Another object of the present invention is to provide a pharmaceutical composition comprising the above compound as an effective component, which has little side effect and is economical, for prevention and treatment of hepatitis C.

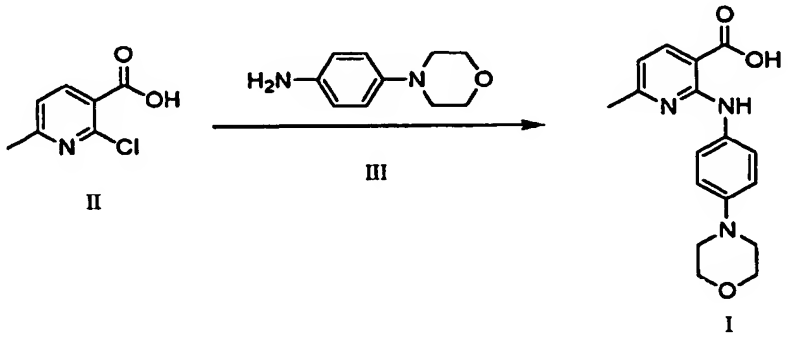
To achieve the above objects, there are provided novel 6-methylpyridine derivatives, represented by the formula 1 shown below and its pharmaceutically acceptable salt.



As aforementioned, the above compounds can be used in form of pharmaceutically acceptable salts. As for that salts, an acid addition salts that are prepared by pharmaceutically acceptable free acids. The compounds with the chemical formula 1 can make pharmaceutically acceptable acid addition salts following the conventional method in the related art. As for free acids, both organic acids and inorganic acids can be used. For instance, inorganic acids

include hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid. Organic acids include citric acid, acetic acid, lactic acid, tartaric acid, maleic acid, fumaric acid, formic acid, propionic acid, oxalic acid, 4-trifluoroacetic acid, benzoic acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, 4-toluenesulfonic acid, glutamic acid or aspartic acid.

Another aspect of the present invention provides a method for preparing 6-methylpyridine derivatives, represented by the following scheme I.



II I

As shown in the above scheme (I), 6-Methylepyridine derivatives of the present invention, represented by chemical formula I, are prepared by reacting 2-chloro-6-methylnicotinic acid of the chemical formula 2 with 4-(4-morforino) aniline of the chemical formula 3. The starting material, i.e. 2-chloro-6-methylnicotinic acid of the chemical formula 2, and the reactant, i.e. 4-(4-morforino) aniline of the chemical formula 3, are commercially available chemicals for anyone to get.

To give more details on the preparation method described above, weak organic bases such as pyridine, 2,6-lutidine, 4-dimethylaminopyridine, *N, N*-dimethylanniline and the like are slowly reacted with organic solvents such as methanol, ethanol, isopropanol, dichloromethane, chloroform, acetonitrile, *N, N*-dimethylformamide, acetone and the like at a temperature in the range of 40 - 80°C for a relatively extended period of time, namely one day to 6 days.

The present invention also provides the pharmaceutical compositions for treatment and prevention of hepatitis C, which contains the 6-methylpyridine derivatives represented by the chemical formula 1 and/or its pharmaceutically acceptable salts as active ingredient.

The compounds of the chemical formula 1 as the therapeutics for hepatitis C may be administered orally as well as through other routes in clinical uses, and can be used in form of general drugs. If it needs to be prepared, a generally used diluent including filler, builder, binder, humectant, dis- integration agent, or detergent (or surfactant) or excipient can be employed. In the meantime, the solid preparation for oral administration includes tablets, pills, powder, granules or capsules. This solid preparation involves more than one compound of the chemical formula 1 and more than one excipient, for example, starch, calcium carbonate, sucrose or lactose, or gelatin. As for the liquid preparation for oral administration, suspension, solution, oily medicine or syrup can be used, but it can also employ a simple diluent, namely water, liquid paraffin, or other kinds of excipient, e.g. humectant, sweetening agent, odorant, or preservative. As for liquid preparation for non-oral administration, sterilized water solution, non-aqueous solvent, suspension or oily medicine. Preferably used non-aqueous solvent and suspension is propylene glycol, polyethylene glycol, vegetable oil like olive oil, and injectable esters like ethyl oleate.

The effective dose of the compound of the chemical formula 1 is controlled depending on the patient's sex, age and condition. In general, it can be dosed to adults 10-1000 mg/day, more preferably 20-500 mg/day, or one to three times dividedly per day.

Detailed description of the preferred embodiment

Now, the present invention is explained in detail by the following

examples. However, the examples are provided for illustration of the present invention not for limitation thereof.

Example : Preparation of 6-methyl-2-[4-(4-morforino) anilino] nicotinic acid

5 g of 2-chloro-6-methylnicotinic acid, 5.45 g of 4-(4-morforino) aniline, and 7.2 mL of pyridine were added to 100 mL of chloroform, and heated at 60°C for five days. When the reaction was completed, the reaction mixture was cooled to room temperature and a little amount of solid extracted from the reaction was filtered and washed with 10 mL of chloroform to remove any impurities therein. The solvent chloroform was concentrated with 60 mL of methanol under reduced pressure and stirred for 1 hour. Then, the organic layer was filtered and washed twice with 10 mL of methanol to give a solid product. The product was dried *in vacuo* at 35 – 45°C to give 7.31 g of the desired compound (89% yield).

m.p.: 220-221°C

^{1}H-NMR (DMSO-d_6), ppm: δ 2.39 (s, 3H), 3.04 (t, 4H), 3.73 (t, 4H), 6.61 (dd, 1H), 6.89 (d, 2H), 7.57 (dd, 2H), 8.05 (dd, 1H), 10.21 (s, 1H)

Experimental example 1: test of inhibitory effect on activity of HCV RNA Polymerase (RNA dependent RNA polymerase, NS5B) *in vitro*

The following *in vitro* experiments were conducted to find out the effect of inhibition activity of compounds of the present invention against HCV RNA Polymerase (RNA dependent RNA polymerase, NS5B).

Construct of recombinant HCV RNA polymerase

HCV RNA polymerase was prepared as follows.

HCV cDNA was obtained from the blood of HCV-1b type HCV patient and NS5B region (1773bps) was amplified by PCR and cloned into pVLHIS, a baculovirus transfer vector, to prepare recombinant transfer vector. The prepared transfer vector and the wild-type AcNPV vector were cotransfected with Sf 9 cell line to yield recombinant baculovirus with the histidine-tagged recombinant vector pVLHIS-NS5B. Sufficiently cultured insect cells were infected with the resulting recombinant baculovirus and cultured in Grace' medium containing 10% FBS for 3 – 4 days. The culture broth was centrifuged to obtain only the infected cells. The cells were washed three times with PBS and resuspended in binding buffer [50mM Na-phosphate (pH 8.0), 30mM NaCl, 10mM imidazole, 1mM DTT, 10% glycerol, 1% NP-40], sonicated and the clearized lysate was obtained. Recombinant NS5B was purified by affinity column chromatography using a Ni-NTA His bind resin (Novagen) to produce pure NS5B protein. The $(His)_6$-tagged NS5B was bound to Ni-NTA resin and washed the binding buffer containing 50mM imidazole. The bound NS5B was eluted with the binding buffer containing imidazole in a step-gradient manner (100 - 300mM). The NS5B protein fractions were dialyzed against buffer [50mM Tris-HCl, 50mM NaCl, 1mM DTT, 5mg $MgCl_2$, 10% glycerol], followed by at -70°C in a small aliquot.

Construct of RNA template containing HCV 3' end (3'-UTR)

The RNA Template containing HCV 3' end (3'-UTR) was prepared as follows.

The 3'UTR cDNA (220bp) of HCV was obtained from 1b HCV RNA of the blood of a hepatitis C patient by PCR and cloned into pcDNA3 vector. Linearized DNA fragment containing 3'-UTR was prepared using the restriction enzyme, i.e. Eco RI and used as a temperate for *in vitro* transcription using T7 RNA ploymerase to prepare RNA fragment containing 3'-UTR.

Measurement of inhibitory activity of compounds of the present invention on recombinant HCV RNA Polymerase *in vitro*

In Vitro inhibitory activity of the compounds of the present invention against recombinant HCV RNA polymerase was measured as follows.

A streptavidin-coated well plate was prepared suitable for the sample to be examined. 25 ㎕ of 2X assay buffer [50mM Tris-Cl (pH 7.5), 100mM NaCl, 10mM $MgCl_2$, 20mM KCl, 1mM EDTA, 1mM DTT] and 10 ㎕ of purified HCV RNA polymerase 200ng and 3'-UTR template RNA were added to each well. Then, 5 ㎕ of the sample to be examined was added to have final concentrations of 10, 1, 0.1 and 0.01㎍/mL . Finally, 10 ㎕ of a reactant solution containing DIG-(digoxigenin)-UTP, biotin-UTP, ATP, CTP, GTP, and UTP as a nucleotide for the ploymerase reaction with the RNA template of HCV 3'-UTR RNA was added to each well. The reaction mixture was incubated at 22°C for 60 minutes. By the action of HCV polymerase, newly generated RNAs including UTP conjugated with biotin and DIG were copied and these new RNAs could bind to streptavidin coated on the well by biotin-conjugated UTP. After completion of the reaction, the plate was washed three times with 200 ㎕ of a washing buffer (pH 7.0, Roche Co.) to remove unreacted substances and impurities. Then, 100 ㎕ of the secondary antibody anti-DIG-POD (peroxidase, Roche Co.) was added to each well and incubated at 37°C for 1 hour. Again, the well plate was washed with the washing buffer. Finally, 100 ㎕ of ABTS^R (Roche Co.) as a POD substrate was added to each well and reacted for 15 to 30 minutes. The optical density (OD) was measured using an ELISA reader (Bio-Tek instrument Co.) at 405nm. The inhibitory effect on the activity of HCV polymerase was calculated by subtracting the OD of the positive control without the sample. The results are shown in Table 1 below.

[Table 1]

Test compound	Inhibition of activity of HCV RNA polymerase (%)			
	10 μg/mL	1 μg/mL	0.1 μg/mL	0.01μg/mL
Example 1	99	82	65	46

As can be seen from the table, it is proved that the compounds according to the present invention show excellent inhibitory effects on activity of HCV RNA polymerase which plays an important role in reproduction of HCV, thereby inhibiting replication of HCV by this property. Also, the compounds according to the present invention can be advantageously used as a therapeutic or prophylactic agent of hepatitis C.

Experimental example 2 : cytotoxicity assay

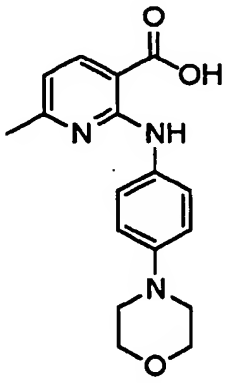
To find out cytotoxicity of 6-methylpyridine derivatives of the chemical formula 1, an *in vitro* experiment was conducted on the basis of the generally known MTT analysis. In result, it was proved that CC_{50} value of every compound employed for the experiment was greater than 100 μg/mL, indicating that they are safe compounds with extremely low cytotoxicity.

Industrial Applicability

As described above, the novel 6-methylpyridine derivatives represented by the chemical formula I have excellent inhibitory effect on replication of hepatitis C virus and low cytotoxicity. Therefore, they can be advantageously used as a therapeutic or prophylactic agent of hepatitis C.

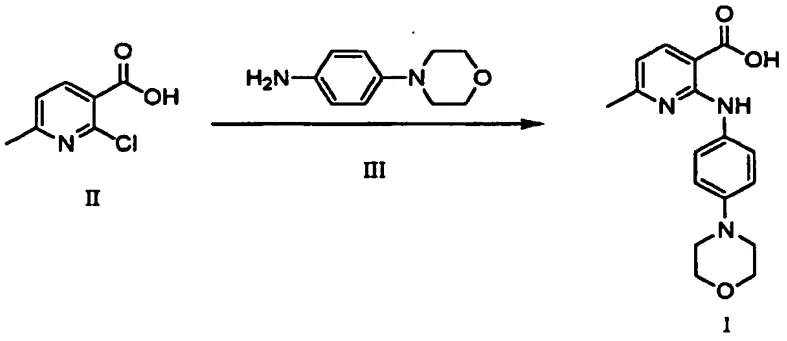
What Is Claimed Is:

1. A 6-methylpyridine derivative, represented by the following formula 1:



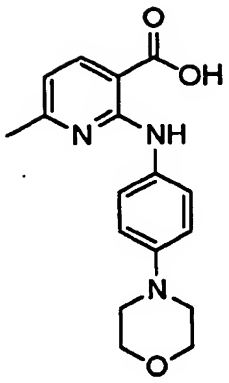
or pharmaceutically acceptable salts thereof.

2. A method for preparing 6-methylpyridine derivatives by reacting 2-chloro-6-methylnicotinic acid of chemical formula II with 4-(4-morforino) aniline of chemical formula III as shown in the following scheme:



II III I

3. A pharmaceutical composition for the treatment and prevention of hepatitis C comprising 6-methylpyridine derivatives, represented by the following formula I:



or pharmaceutically acceptable salts thereof as an active ingredient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2003/002034

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 413/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 07 C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and Application for Inventions Since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS online(STN), Medline, Delphion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0178648 A2 (Dong Wha Pharm. Ind. Co., Ltd.) 25.Oct.2001 See whole document (Page 14, Compound 4)	1-3
A	EP 0187705 A2 (Norwich Eaton Pharmaceuticals, Inc.) 16.July 1986 See whole document	1-3
A	US 3878206 (Morton-Norwich Products, Inc.) 15. April 1975 See whole document	1-3
A	H.R. Snyder, Jr., C.F. Spencer and R. Freedman, Imidazo[4,5-f]quinolines III:Antibacterial 7-Methyl-9-(substituted Arylamino)imidazo[4,5-f]quinolines, Journal of Pharmaceutical Sciences, 1997, Vol.66(8), pp1204-6	1-3

☐ Further documents are listed in the continuation of Box C.

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